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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

To:

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GRANDE BRETAGNE

Date of mailing *(day/month/year)*	21.08.2000
Applicant's or agent's file reference 33377-00/PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/09486	29/04/1999	29/04/1998

Applicant
AMERICAN CYANAMID COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Vullo, C Tel.+49 89 2399-8061

Form PCT/IPEA/416 (July 1992)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
33377-00/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/09486	29/04/1999	29/04/1998
International Patent Classification (IPC) or national classification and IPC C12N15/31		
Applicant AMERICAN CYANAMID COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/11/1999	21.08.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bretherick, J Telephone No. +49 89 2399 8415

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/09486

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-85 as originally filed

Claims, No.:

1-42 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,6,10,11,13,14,16-42
	No:	Claims	1-4,7-9,12,15
Inventive step (IS)	Yes:	Claims	5,6,11,14,16-42
	No:	Claims	1-4,7-9,10,12,13,15
Industrial applicability (IA)	Yes:	Claims	1-8,15-29,31-42
	No:	Claims	9-14,30, opinion reserved

2. Citations and explanations

   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. **Regarding Part IV:**

The International Examining Authority agrees with the findings of the International Searching Authority on the lack of unity under R. 13.1 PCT of the current application.

The application consists of 4 separate invention groups according to the claims:

1. Claims 1,15 (all partially); 2,7,8,9,13 (all completely)

A vaccine composition comprising isolated and purified recombinantly-expressed pilin protein from the species Neisseria gonorrhoea, associated adjuvants, methods of immunisation with same and preparation thereof.

2. Claims 1,3,10,12,15 (all partially); 4 (completely).

A vaccine composition comprising isolated and purified recombinantly-expressed class I pilin protein from the species N. meningiditis, methods of immunisation and preparation.

3. Claims 1,3,10,12,15 (all partially); 5 (completely)

A vaccine composition comprising isolated and purified recombinantly-expressed class II pilin protein from the species Neisseria meningiditis, methods of immunisation and preparation.

4. Claims 1,15 (all partially); 6,11,14, 16-42 (all completely)

A vaccine composition comprising isolated and purified recombinantly-expressed chimeric pilin protein of Neisseria gonorrhoea and class I N. meningiditis having the amino acid sequence 1-167 (or 8-167 after maturation) of SEQ ID NO:2 or a biologically equivalent amino acid sequence, methods of immunisation and preparation. Coding nucleic acid according to SEQ ID NO:1 and variants thereof methods of production and the isolated, purified chimeric pilin.

Same as above except with class II protein of N. meningiditis having the amino acid sequence 1-170 (or 8-170 after maturation) of SEQ ID NO:4 or a biologically equivalent amino acid sequence, isolated purified nucleic acids and variants thereof (SEQ. ID. NO:3) the isolated purified chimeric pilin protein.

Vaccines for protection against disease caused by N. gonorrhoea and/or N. meningiditis based on pilin proteins are art. For example, WO9408013 discloses vaccines based on recombinantly-expressed class I pilin from N. meningiditis. Vaccines based upon pilin proteins of N. gonorrhoea are disclosed in, for example, US4443431.

In the light of this art the problem underlying the present problem is considered to be the provision of (further) components for inclusion in vaccines to protect against the diseases caused by N. gonorrhoea or all serotypes of N. meningiditis. The solutions to this problem are classed according to the above invention groups.

The sequences of the above solutions are all fundamentally different and the commonalities such as vaccine composition, adjuvant and protein production, vaccination methods are all art **per se**. There are no additional special technical features which might form a common unifying link between the invention groups.

A lack of unity under R. 13.1 PCT thus exists.

2. **Regarding Part V, Art. 33 PCT:**

a. Vaccine compositions comprising recombinant pilin proteins of Class I from **Neisseria** are cited frequently in the art. For example, WO93/11791 discloses polypeptides from **N. gonorrhoeae** and **N. meningiditis,** (Fig 9. and 10 respectively) which are to be suspended in a suitable pharmaceutical carrier and used as a vaccine (page 7, lines 23-26). pilE products of **N. meningiditis** class I pilins are disclosed in WO94/08013 and are proposed to provide immunological protection against the genus **Neisseria,** and are also to be formulated as vaccines in formulations which involve the "classical" use of adjuvants known to the skilled person (such as those mentioned in claim 8).

The incorporation of specific cyanogen bromide cleaved fragments of class I pilin from **N. gonorrhoeae** into vaccine formulations to provide immunological protection against this species is disclosed in US patent 4,443,431. These polypeptides are not distinguishable from those which could be synthesised using recombinant technology.

The subject-matter of claims 1-4, 7-9, 12, 15 is thus not novel under Art. 33(1)(3) PCT.

b. Class II proteins are known from N. meningitidis, (see for example, Aho et al. (1997) Infection and Immunity, Vol. 65, pp. 2613-2620). These might form the logical basis for a vaccine. In view of this an inventive step cannot be accorded to current claim 5, since it is known that vaccination using any particular pilin protein can induce strain-restricted immunity (see for example, acknowledgement of the art in the current description, page 9, lines 17-21).

c. Claim 10 does not involve an inventive step. Cross-reactivity between **N. gonorrhoeae** and **N. meningiditis** class I pilin proteins is known to exist. The use of a generic pilin protein from **N. meningiditis** is to immunise against N. meningiditis is thus considered to be obvious speculation, in the absence of any technical information pertaining to the region structure of the protein **per se** and in view of the teaching of WO94/08013 expressed **supra**. This also applies, mutatis mutandis to the subject-matter of claim 13, directed to using the protein derived from **N. gonorrhoeae** to vaccinate against **N. meningiditis**.

d. Subject to the **caveat** expressed in the notes to Part VIII below, the remaining claimed subject-matter appears to be novel and to involve an inventive step. This deals with unique sequences encoding class I fusion proteins of **N. gonorrhoeae** and **N. meningiditis** which are not derived from any art in an obvious manner.

e. Claims 9-14 and 30 are directed towards methods of therapy and/or prophylaxis. An opinion on the industrial applicability of these claims is reserved, since there is no unified policy within the PCT on this matter.

3. **Regarding Part VIII, Art. 6 PCT:**

References within claims 15-17, 19, 20, 31, 32, 34, to hybridisation conditions without indicating that the function of the protein be restricted either by function or structure in some way renders the DNA unclear.

Similarly references in the claims to "or biologically equivalent amino acid sequence thereof" does not define the protein or ecoding DNA in clear terms, since what is meant by this is not defined within the claims **per se**.